DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 13-402/S-081

JUL 23 1999

Merck Research Laboratories
Attention: Larry P. Bell, M.D.
P.O. Box 4, BLA-20
West Point, PA 19486-004

Dear Dr. Bell:

Please refer to your supplemental new drug application dated October 20, 1997 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aldoril (methyldopa/hydrochlorothiazide) 250/15, 250/25, 500/30 and 500/50 mg Tablets.

We acknowledge receipt of your May 12, 1999 submission.

This supplemental new drug application provides for final printed labeling revised as follows:

1. The following has been added to the **PRECAUTIONS**/Drug Interactions section:

   When methyldopa and lithium are given concomitantly the patient should be carefully monitored for symptoms of lithium toxicity. Read the prescribing information for lithium preparations.
   Several studies demonstrate a decrease in the bioavailability of methyldopa when it is ingested with ferrous sulfate or ferrous gluconate. This may adversely affect blood pressure control in patients treated with methyldopa. Coadministration of methyldopa with ferrous sulfate or ferrous gluconate is not recommended.

2. The last sentence of the first paragraph in the **DOSAGE AND ADMINISTRATION** section has been changed from:

   For those patients requiring higher doses, one tablet of ALDORIL D30 or ALDORIL D50 once daily may be used.

   to:

   Alternatively, one tablet of ALDORIL D30 or ALDORIL D50 once daily may be used. Hydrochlorothiazide doses greater that 50 mg daily should be avoided.

   The second paragraph in the **DOSAGE AND ADMINISTRATION** section has been changed from:

Patients usually do not require doses of hydrochlorothiazide in excess of 50 mg daily when combined with other antihypertensive agents. The usual daily dosage of methyldopa is 500 mg to 2 g. To minimize the sedation associated with methyldopa, start dosage increases in the evening.

to:

Hydrochlorothiazide can be given at doses of 12.5 to 50 mg per day when used alone. The usual daily dosage of methyldopa is 500 mg to 2 g. To minimize the sedation associated with methyldopa, start dosage increases in the evening. The maximum recommended daily dose of methyldopa is 3 g.

3. The following sentence has been removed from the third paragraph of the **DOSAGE AND ADMINISTRATION:**

   The maximum recommended daily dose of methyldopa is 3 g and of hydrochlorothiazide is 200 mg.

4. Under the **HOW SUPPLIED** section, the following has been deleted:

   NDC 0006-0423-82 bottles of 1000.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling included in your May 12, 1999 submission. Accordingly, the supplemental application is approved effective on the date of this letter.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Mr. David Roeder
Regulatory Project Manager
(301)594-5300

Sincerely yours,

Raymond J. Lipicky, M.D.
Director
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Office of Drug Evaluation I
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